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REPORT

CD NO.

STAT

COUNTRY	USSR	DATE OF INFORMATION	1953
SUBJECT	Scientific - Chemistry, antituberculous drugs; Medicine, tuberculosis		
HOW PUBLISHED	Bimonthly periodical	DATE DIST.	30 Oct 1953
WHERE PUBLISHED	Kiev	NO. OF PAGES	3
DATE PUBLISHED	Jun 1953		
LANGUAGE	Russian	SUPPLEMENT TO REPORT NO.	

THIS IS UNEVALUATED INFORMATION

SOURCE Ukrainskiy Khimicheskiy Zhurnal, Vol XIX, No 3, pp 239-246

USSR WORK ON DRUGS ACTIVE AGAINST TUBERCULOSIS

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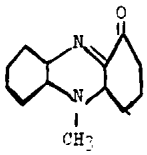
After the discovery had been made that 4,4'-diaminodiphenylsulfone has antituberculous activity, both USSR and foreign chemists carried out a systematic investigation of aromatic aminosulfones with a view toward utilizing substances of this class against tuberculosis. Some of these substances were effective, but the results were not quite up to expectations.

In the first years after World War II, V. S. Derkach, professor at the Khar'kov Medical Institute and Corresponding Member of the Academy of Medical Sciences USSR, discovered that the natural antibiotic pyocyanine (I) has a high antituberculous activity.



(I)

At the request of Derkach, pyocyanine and a number of its homologs and analogs were synthesized at the Institute of Organic Chemistry, Academy of Sciences Ukrainian SSR. Pyocyanine turned out to be rather toxic, but one of its homologs, which was name sanazin, proved to be less toxic and more active than pyocyanine. Sanazin is a blue crystalline substance easily soluble in water. It has found application as a remedy for external use and as a drug for intravenous injections. Sanazin proved to be particularly effective for the treatment of tuberculosis of the eyes. [1]

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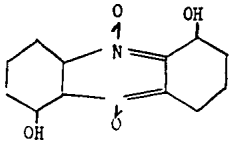
In connection with the work on pyocyanine and sanazin, the Institute of Organic Chemistry, Academy of Sciences Ukrainian SSR, carried out a systematic investigation of a number of phenazine derivatives containing hydroxy, alkoxy, and halogen groups. A. I. Kiprianov, S. B. Serebryanyy, and Y. P. Chernetskiy succeeded in establishing the constitution of one of the natural antibiotics of the phenazine series, namely iodinin (II), which is the pigment of Bacterium iodinum.



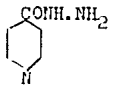
(II)

Subsequently, these investigators synthesized iodinin. [2] Iodinin has a rather high antituberculous activity, but this activity is eliminated by blood serum.

Since Lehman had discovered in 1946 that para-aminosalicylic acid (PASK) exerts a bacteriostatic effect on tuberculosis bacilli [3], this substance rapidly becomes the most important drug for the treatment of tuberculosis and remained prominent for a certain period. The demand for para-aminosalicylic acid in the USSR was quickly satisfied as a result of the organization of an industrial production of this chemical.

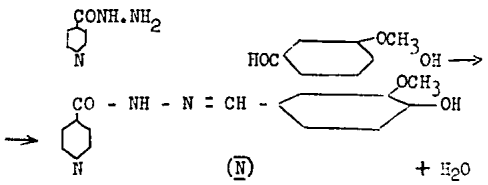
Almost simultaneously with the introduction of PASK, streptomycin began to be used on an extensive scale in the USSR as a remedy for tuberculosis.

In the beginning of 1952, a very important event took place in chemotherapy. Almost simultaneously, USSR and foreign journals published communications on a new, highly active antitubercular drug, i.e., the hydrazide of isonicotinic acid (III). The properties of isonicotinic acid hydrazide were investigated in the USSR by M. N. Shchukina and her collaborators. [4] This drug was described by H. Fox abroad. [5]

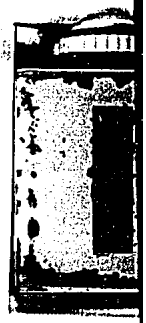


(III)

According to Shchukina, the hydrazide of isonicotinic acid suppresses the development of tuberculosis bacilli even when it has been diluted in a ratio as high as one to 16 million. The activity of this drug is practically not lowered at all in the presence of blood serum. In vitro and in animal experiments, isonicotinic acid hydrazide has been found to surpass para-aminosalicylic acid, tibon (tibione; para-acetylaminobenzaldehyde thiosemicarbazone), and apparently also streptomycin. The toxicity of this substance is low. As demonstrated by Shchukina, the toxicity can be lowered still further if hydrazones (products of the condensation of the hydrazide with aldehydes) are used instead of the hydrazide. Shchukina has described 16 substances of this type. As an example one may mention the hydrazone (IV) obtained by condensation with vanillin:



(IV)



Hydrazone IV is active in a dilution of one to 16 million. Its toxicity is so low that a mouse survives a single dose of more than 40 mg. One of these hydrazones is already being manufactured in the USSR under the name of phthivazid and is used by medical institutions.

The chemotherapeutic specificity of isonicotinic acid hydrazide (III) is remarkable. According to Shchukina's data, the metaisomer of this substance is almost inactive as compared with the paraderivative (III). The hydrazones of the metacompound also do not exhibit much activity.

Although the discovery of the antituberculous activity of isonicotinic acid hydrazide and of the hydrazones derived from it represents a significant advance, it is necessary to continue the search for other drugs that are active against tuberculosis. In view of the fact that tuberculosis bacilli are capable of acquiring resistance to chemotherapeutic agents, several highly effective drugs rather than a single one must be available for medical use.

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